Decision Memo for Autologous Blood-Derived Products for Chronic Non-Healing Wounds (CAG-00190N)

Decision Summary

CMS has determined that the evidence is adequate to conclude that autologous platelet-derived growth factor (PDGF) in a platelet poor plasma does not improve healing in chronic non-healing cutaneous wounds and, therefore, is not reasonable and necessary. CMS will continue noncoverage of this treatment.

CMS has determined, in the absence of specific evidence of benefit that there is not sufficient evidence to conclude that autologous platelet rich plasma is reasonable and necessary for the treatment of chronic non-healing cutaneous wounds. In light of the absence of data on the health outcomes of this treatment, we intend to issue a national noncoverage determination for use of this product except when used in accordance with the clinical trial policy defined in section 30-1 of the Coverage Issues Manual.

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Decision Memo

This decision memorandum does not constitute a national coverage determination (NCD). It states the intent of the Centers for Medicare & Medicaid Services (CMS) to issue an NCD. Prior to any new or modified policy taking effect, CMS must first issue a manual instruction, program memorandum, CMS ruling or Federal Register Notice, giving specific directions to our claims processing contractors. That issuance, which includes an effective date, is the NCD. If appropriate, the Agency must also change billing and claims processing systems and issue related instructions to allow for payment. The NCD will be published in the Medicare Coverage Issues Manual. Policy changes become effective as of the date listed in the transmittal that announces the Coverage Issues Manual revision.

To: Administrative File: (CAG-00190N)

Autologous Blood-Derived Products for Chronic Non-Healing Wounds

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Subject: Coverage Decision Memorandum for Autologous Blood-Derived Products for Chronic Non-Healing

Wounds

Date: December 15, 2003

I. Decision

CMS has determined that the evidence is adequate to conclude that autologous platelet-derived growth factor (PDGF) in a platelet poor plasma does not improve healing in chronic non-healing cutaneous wounds and, therefore, is not reasonable and necessary. CMS will continue noncoverage of this treatment.

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II. Background

A wound is a disruption of normal anatomic structure and function and can range from a simple scratch to an interruption that goes through tissue and muscle down to bone. Acute wounds are wounds of relatively new onset that heal in an orderly fashion, first by reestablishing epithelial integrity, then by laying down new collagen to strengthen the damaged tissue. The result is re-establishment of anatomic and functional integrity. Fortunately, most wounds are acute wounds that heal rapidly and uneventfully.

The process of wound healing involves an integrated series of cellular, physiologic, biochemical, and molecular events. The stages of wound healing are defined as inflammatory, proliferative, and remodeling. The inflammatory phase is characterized by platelet accumulation, coagulation, and leukocyte migration into the wound site. During this phase, the platelets adhere to collagen to form a vascular plug and the leukocytes, along with macrophages, begin removing cellular debris and bacteria. This inflammatory phase occurs during the first three to four days after a wound presents. The cellular interactions in this phase help to provide a temporary stable wound environment.

The proliferative phase, also termed fibroblastic, is characterized by regeneration of epidermis, angiogenesis, and the proliferation of fibroblast that forms collagen. Angiogenesis, the formation of a new vascular supply, is important for allowing the nutrition required in the healing process to invade the wound area. Type III collagen is produced during this phase and is instrumental in decreasing the wound size through contraction. The reepithelialization helps to restore the cutaneous barrier. All of these physiologic events normally occur during the 10 to 14 day period after a wound presents.

The third and final phase of wound healing, the remodeling phase, takes place from a period of months up to 2 years. This phase is characterized by collagen synthesis and degradation. The type III collagen produced during the proliferative phase is replaced by type I collagen. Continued wound contraction is also seen during this phase. Contractile forces are produced by contractile proteins that are present in the fibroblast of granulation tissue. At the end of remodeling, the resulting scar tissue is approximately only 80% the strength of normal skin2.

The stages of wound healing are sequential in the normal healing process of acute wounds. Many chronic wounds fail to complete all the stages of normal wound healing. When the healing process fails to progress properly and the wound persists for longer than one month, it may be described as a chronic wound. In chronic wounds, the healing process is disrupted by some underlying abnormality that prolongs the inflammatory phase, resulting in poor anatomic and functional outcome. Common underlying abnormalities include diabetes, abnormal external pressures and arterial, or venous circulatory insufficiency.

Since the etiology of wounds vary, the most effective therapy may vary as well. For example, the etiology of a pressure ulcer relates to unrelieved pressure on the skin, whereas the origin of a diabetic ulcer has other etiologies. Therefore, it is difficult to generalize the findings from studies on therapy from one type of ulcer to another type. According to the "Guidance for Industry-Chronic Cutaneous Ulcer and Burn Wounds-Developing Products for Treatment," the Food and Drug Administration (FDA) states that "Wounds differ pathophysiologically, making it difficult-if not impossible-to generalize results obtained from a trial conducted in patients with one type of wound to those with another wound type. Separate safety and efficacy data should be submitted for each wound type for which an indication is sought."

Wound care must be directed at providing an environment in which the body can effectively carry out the healing process. Conventional or standard therapy for chronic wounds involves local wound care as well as systemic measures. Standard care considerations to promote wound healing include debridement or removal of necrotic tissue, wound cleansing and dressings that promote a moist wound environment. Systemic treatments include the use of antibiotics to control infection and optimizing nutritional status. Early concepts in wound management involved soaking the wound in antiseptics to kill bacteria and then covering the wound with a dry dressing. As the biology of wound healing has become better understood, a variety of wound care strategies and products have been developed to help aid the healing process. Various new dressings such as alginates, hydrogels, films, and foam products are now used. Additionally, newer techniques such as negative pressure dressings, radiant heat, electrical stimulation and hyperbaric oxygen are also being investigated.

There are other conventional therapeutic modalities that may apply to certain subgroups of patients depending on their type of wound. Specific conventional therapies for venous ulcers include the use of compression devices aimed at decreasing venous stasis. Patients that have pressure ulcers require frequent repositioning to redistribute the pressure that is causing the ulcers. Good glucose control for diabetic foot ulcers and establishing adequate circulation for arterial ulcers are other ulcer-specific therapies.

The multitude of wound care regimens demonstrates the complexity of wound care management and the lack of one, universally proven treatment strategy. Knowledge of the pathophysiology of healing combined with realistic patient outcomes will help guide the clinician in choosing the wound care treatment plan. Lait and Smith reported that no single wound dressing is sufficient for all types of wounds and few are ideally suited for the treatment of a single wound through all phases of healing.⁵

Some wound care specialists have proposed that chronic wounds do not heal due to a lack of vital growth factors that are believed to be deficient in chronic wounds. Several sources noted by Payne have proposed that this deficiency is due to repeated trauma, ischemia, and infection that increases the level of proinflammatory cytokines, increases the level of matrix metalloproteinases, decreases the presence of tissue inhibitors of metalloproteins, and lowers the level of growth factors.

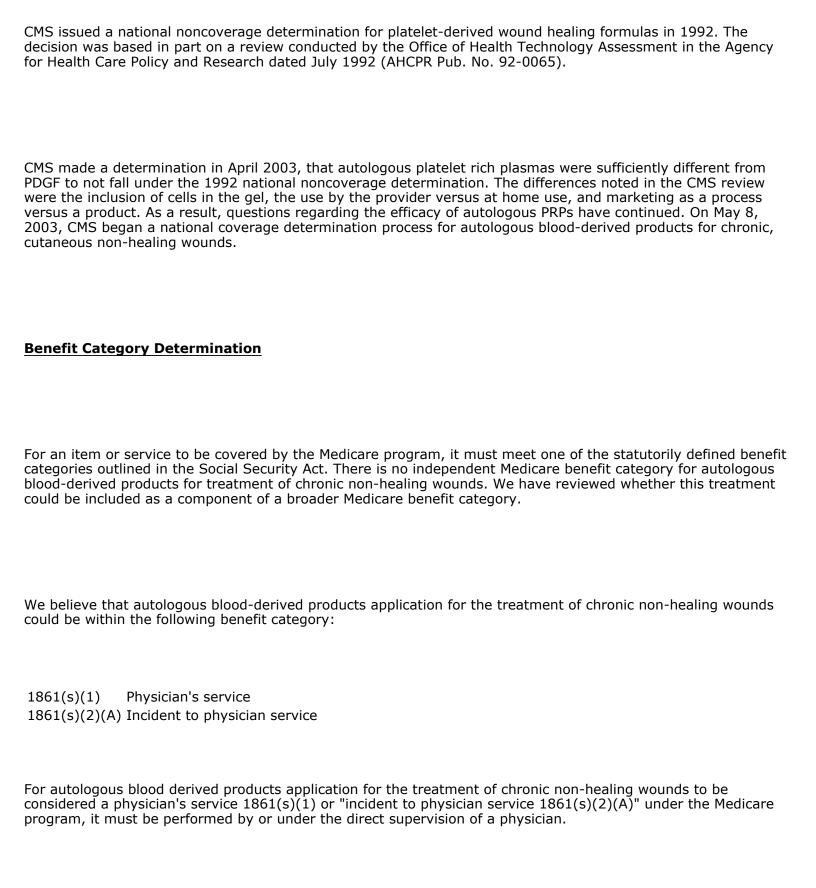
Originally, it was thought that platelets were important only for clot formation. However, it is now clear that platelets contain a large number of growth factors. The exact number and purpose of all of the growth factors is not known. Four growth factors are mostly frequently cited. The first is the platelet derived angiogenesis factor that causes new capillary formation from the existing microvasculature. Platelet-derived epidermal growth factor and platelet factor 4 (considered to be a chemoattractant for neutrophils) have also been identified. The fourth type is platelet-derived growth factor (PDGF), which is a potent fibroblast mitogen and chemoattractant.

With this knowledge, Dr. David L. Knighton developed, in 1985, a system to obtain multiple growth factors from platelets and started treating patients at the University of Minnesota. A retrospective study based on the first patients treated with PDGF was published in 1986. 10 The first prospective trial was then conducted by Knighton et al. and the results were published in 1990. 11 Dr. Knighton obtained a patent in 1992 on products released from platelets (i.e., platelet releasate) that are used for tissue repair. Procuren Solution® produced by CuraTech (which later became Curative Health Services) was available throughout the United States through 150 wound care centers starting in 1986. Marketing of Procuren Solution® ceased in 2001. However, various PDGF products, which contain multiple proteins like Procuren but do not contain cells like platelet rich plasma, are in use for patient care.

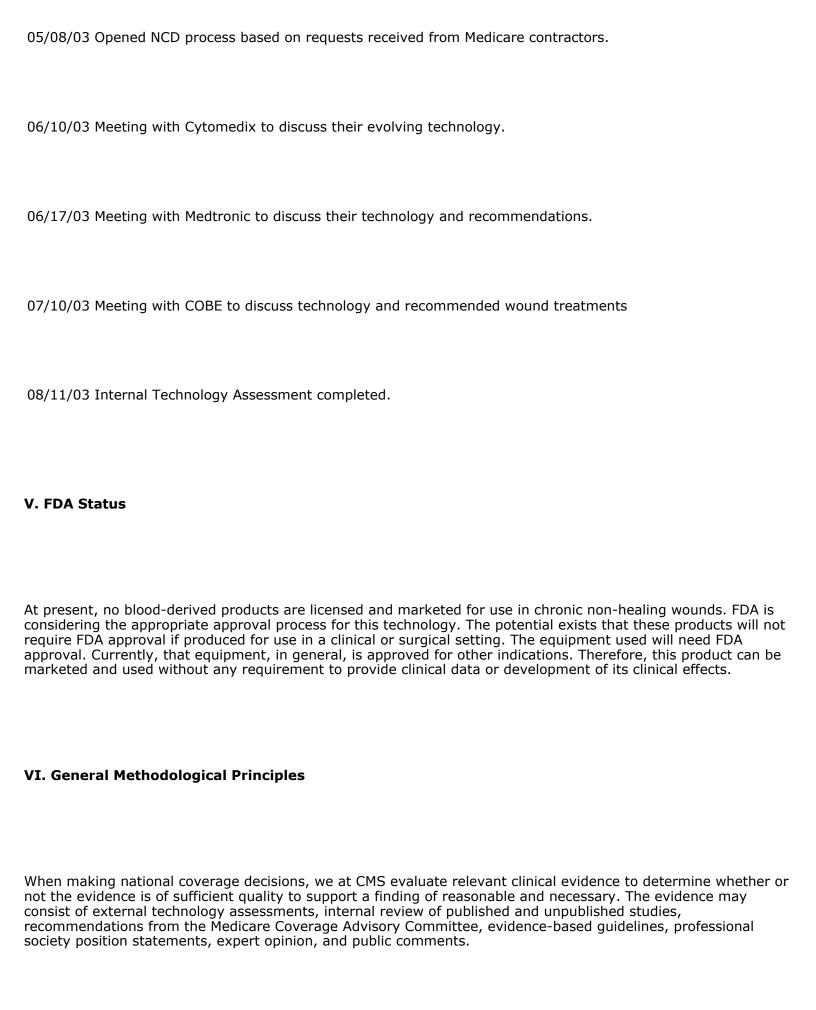
In 1997, FDA approved the biologics license application of Ortho-McNeil Johnson Pharmaceuticals, Inc. to market Regranex® (becaplermin) Gel 0.01%. The recombinant human platelet-derived growth factor-BB (rhPDGF-BB) was approved for the treatment of lower extremity diabetic neuropathic ulcers that extend into subcutaneous tissue or beyond and have an adequate blood supply. It was not approved for superficial ulcers that do not extend through the dermis into subcutaneous tissue or ischemic diabetic ulcers. Since becaplermin is not an autologous product, we have elected to not address this product in this decision memorandum.

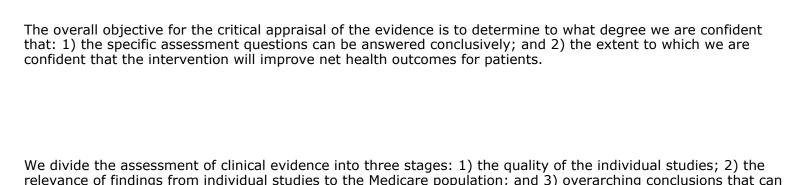
In an attempt to improve the healing process, wound specialists have become more interested in autologous platelet rich plasma (PRP) produced by an apheresis process first developed by Charles Worden in 1998. In this process, autologous blood (blood donated by the patient) is centrifuged to produce a concentrate high in both platelets and plasma proteins. Individual growth factors are not identified or separated during this process. Additives are used to change the consistency of the product. Autologous PRP has been used for a variety of purposes such as an adhesive in plastic surgery and filler for acute wounds. It is also now being used on chronic wounds. PRP is different from earlier products in that it contains whole cells including white cells, red cells, plasma, platelets, fibrinogen, stem cells, macrophages, and fibroblasts and is used by physicians in a clinical or surgical setting. PDGF does not contain cells and was previously marketed as a product to be used by patients at home. Both PDGF and PRP gels are derived from the patient's own blood.

III. History of Medicare Coverage



IV. Timeline of Recent Activities





The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

be drawn from the body of the evidence on the direction and magnitude of the intervention's risks and benefits.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were
 assigned (intervention or control). This is important especially in subjective outcomes, such as pain or
 quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by
 either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study, or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population



CMS determines whether an intervention is reasonable and necessary by evaluating its risks and benefits. For all determinations, CMS evaluates whether reported benefits translate into improved net health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an

3. Assessing the Relative Magnitude of Risks and Benefits

intervention or technology's benefits and risk of harm to Medicare beneficiaries.

VII.	Evidence

A. Introduction:

The following summary represents the body of evidence for this decision. The evidence reviewed about the use of autologous, blood-derived wound healing products for chronic, non-healing cutaneous wounds includes the peer-reviewed literature evaluated by both external and internal technology assessment and external expert opinion.

It is important to note that Procuren is no longer commercially available. However, various platelet poor plasma products, which contain multiple proteins like Procuren but do not contain cells like platelet rich plasma, are in use for patient care.

The health outcome of interest to CMS in this decision memorandum is the impact of autologous, blood-derived wound healing products for chronic, non-healing wounds on the frequency of 100% epithelialization (i.e., complete wound healing). As noted by Payne, 12 long-term outcomes should be the desired outcome for wound care. He further noted that the Wound Healing Society has stated that acceptable healing must result in sustained anatomical and functional integrity, and that recurrence rates must be taken into account when considering the usefulness of wound therapy such as growth factors.

B. Discussion of evidence reviewed
 The development of an assessment in support of Medicare coverage decisions is based on the same general question for almost all requests: "Is the evidence sufficient to conclude that the application of the technology under study will improve final health outcomes for Medicare patients?"
The formulation of specific questions for the assessment recognizes that the effect of an intervention can depend substantially on how it is delivered, to whom it is applied, the alternatives with which it is being compared, and the delivery setting. In order to appraise the net health outcomes of autologous, blood-derived wound healing products for chronic, non-healing wounds in comparison with standard wound therapy and identify any relevant patient and facility selection criteria, CMS sought to address the following question:
Is there evidence of adequate methodological quality to conclude that the use of autologous, blood-derived wound healing products for chronic, non-healing wounds significantly and reliably improves 100% healing in the Medicare population?
2. External technology assessment
An external technology assessment was published by the Agency for Health Care Policy and Research Office of Health Technology Assessment in July 1992, titled "Procuren: A Platelet-Derived Wound Healing Formula." 13 They conducted a literature search and reviewed responses received from professionals involved with the study of growth factors. Only three published articles were found about platelet-derived wound healing formulas. Two were uncontrolled and the only controlled study was by Knighton in 1990. 14 For that article, the study quotes the author as saying "the study sample was small and randomization was not stratified according to diagnostic groups". They found that it was impossible to determine the clinical effectiveness of Procuren and suggested further research.
3. Internal technology assessment

We did a search on PubMed using the following terminology: Safeblood, Procuren, Autologel, growth factor, autologous, ulcer healing, wound healing, platelet derived, diabetic wound healing, wound treatments, ulcer treatments, blood derived, blood products, platelet grafting, autologous platelet rich plasma, wound care, and ulcer care. We did limit our search to articles that were in English and related to humans. We did not limit our search to recent articles (those published within the last 10 years) because we wanted to review the literature that was available when the current national coverage determination was made in 1992. In addition, we did not limit our search to studies conducted in the United States and/or studies using more advanced methodology as described in Section VI to assure that we obtained a broad understanding of the subject matter. The large number of articles identified for analysis was further narrowed by eliminating articles concerning homologous products, becaplermin, non-cutaneous (non-skin) use, and those articles not stating study results such as editorials. We also read all additional articles submitted as part of the public comment process.

Autologous platelet rich plasma

Numerous literature articles were submitted by external constituencies and a comprehensive literature search was conducted by CMS, but no evidence was found that focused on the use of platelet rich plasma in chronic, cutaneous non-healing wounds. CMS's review of the literature did locate articles with evidence on acute surgical wounds, such as coronary artery bypass grafting, maxillary sinus surgery, and facial reconstruction. However, the focus of many of these articles was on hemostasis of acute wounds and not specifically wound healing. In addition, as stated in our background section, acute surgical wounds sequentially complete all the stages of healing and, unless demonstrated otherwise by appropriate research, are assumed to respond differently to various therapies. Therefore, CMS did not include literature on acute wounds in our analysis.

Autologous platelet derived growth factors

As noted in Appendix 1, seven articles on platelet-derived growth factors were selected. Three of these articles, Glover, et al (1997), Knighton, et al (1989), and Margolis, et al (2001), were retrospective in nature and only one of these studies, Margolis, et al (2001), had any statistical weighting to control for the lack of a randomized design.

Glover, et al. (1997) reported a retrospective, uncontrolled, four-year study in wound care centers in 39 hospitals evaluating the effectiveness of platelet releasate for a variety of types of wounds. The frequency of 100% epithelialization was 65.7% and 50.8% in the treatment and control groups, respectively (p<0.00001).



Patients were assessed every 2-3 weeks. The degree of epithelialization was determined visually at each visit. Wound dimensions were determined by direct measurement and photography. Wound area equaled the remaining unepithelialized wound surface. Wound duration was statistically significantly greater in the treatment group (119 \pm 114 weeks) than in the control group (47 \pm 63 weeks, p=0.04 (a clarification for a standard deviation greater than the mean was not provided in the article).

The frequency of 100% epithelialization at 8 weeks in the Knighton trial was 17/21 (81%) of wounds in the active treatment group and 2/13 (15%) of wounds in the control group. Intention to treat results and statistical analysis were not reported. The time to 100% epithelialization was 8.6 ± 4.2 weeks in the active treatment group and 15 \pm 4.5 weeks in the control group (p=0.002).

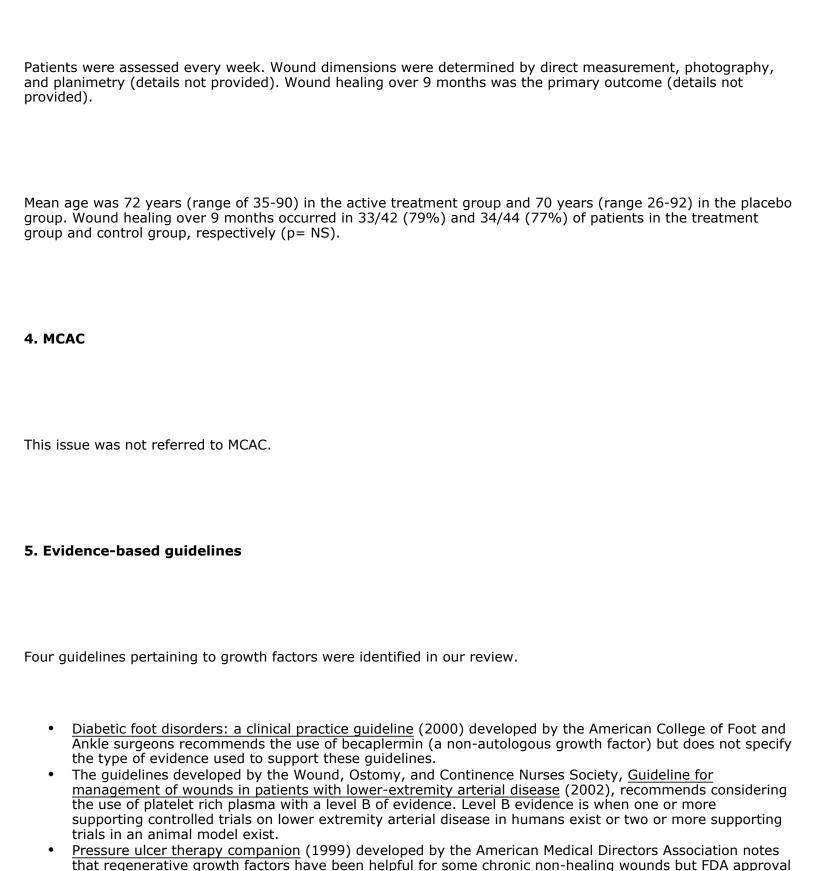
Krupski, et al (1991) conducted a prospective, double-blinded, randomized, placebo-controlled, 2-arm trial. Stratified randomization by wound type was not performed. Wounds had to be greater than 8 weeks in duration and less than 100 cm² in area or less than 50,000 cm³ in volume. Ten patients were randomized to debridement followed by active treatment with PDGF releasate (dose not specified) every 12 hours; 8 patients were randomized to a debridement plus normal saline placebo every 12 hours. The patient applied the treatment. Standard wound care was provided to all patients as needed.

Patients were assessed every week. Wound dimensions were determined by directly measuring length and width and then calculating the surface area and volume. Photography was used to validate the direct measurements. Rate of healing was the primary outcome and was determined by calculating the differences between initial and final wound areas and volumes and dividing this figure by the number of weeks of therapy. A healed wound was defined as a wound visually determined to be completely covered with new epithelium. The frequency of 100% epithelialization at 12 weeks was also determined.

A total of 26 wounds were treated; 17 with PDGF and the remaining with placebo. Twenty-eight percent of the patients had venous insufficiency, 72% had occlusive peripheral vascular disease, and 78% had diabetes. There were no statistically significant differences in distribution of wound types or any other patient variable between active treatment and control groups. Mean age in the active treatment group was 66 ± 5 years and 67 ± 4.5 years in the control group.

The frequency of 100% epithelialization at 12 weeks was 4/17 wounds (24%) in the active treatment group and 3/9 wounds (33%) in the control group (p= NS). The healing rate by surface area was -4.3 ± 12.2 cm2/week and 1.9 ± 2.7 cm2/week in the active treatment and control groups, respectively (p= NS). The healing rate by volume was -0.1 ± 0.7 cm3/week and 0.1 ± 0.2 cm3/week in the active treatment and control groups, respectively (p= NS). Hence, while the wound minimally decreased in size in the control group, the wound actually increased in size in the treatment group.

In Stacey, et al (2000), 86 patients with wounds due to venous insufficiency were studied in a prospective, double-blinded, randomized, placebo-controlled, 2-arm trial. The duration and extent of wounds were not specified. Forty-two patients were randomized to active treatment with twice weekly PDGF lysate (dose not specified). Forty-four patients were randomized to twice weekly placebo. Treatment was applied by a clinician in a wound clinic until the wound healed or for no more than 9 months. Number of wounds and the specifics of standard of care were not reported.



is still pending for pressure ulcers. The majority of recommendations in these guidelines are based on

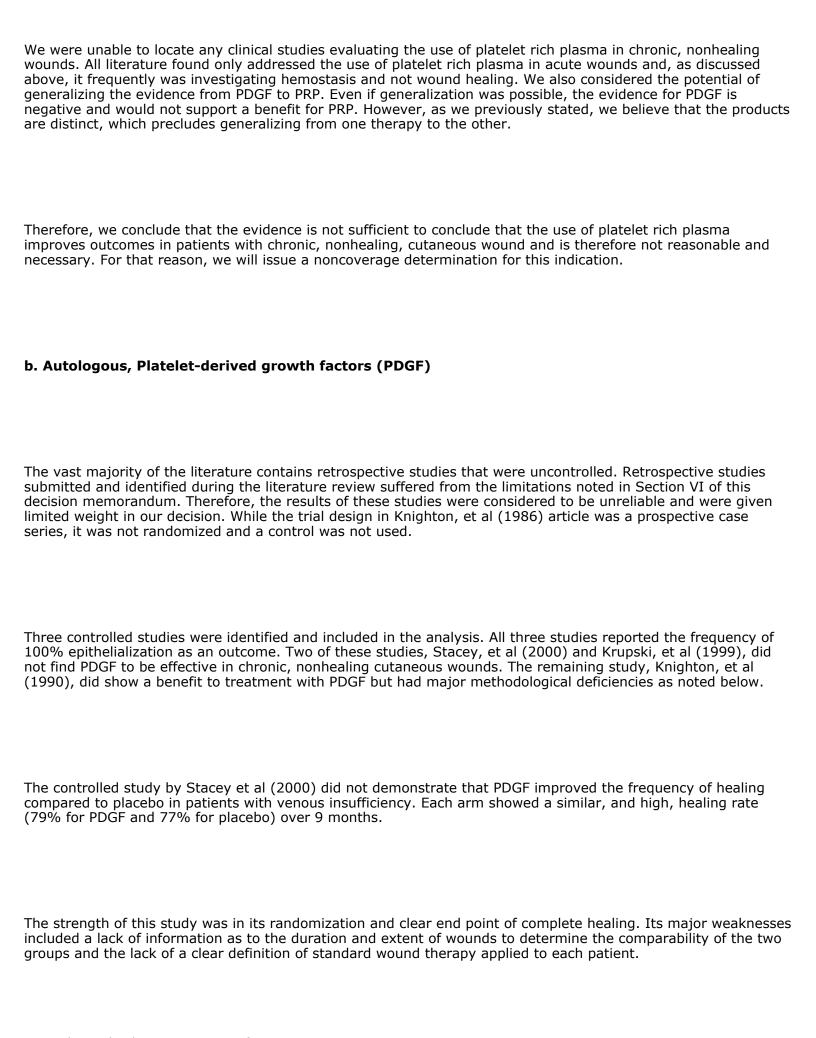
The guidelines developed by the Agency for Healthcare Research and Quality (a Federal Government Agency, <u>Treatment of pressure ulcers</u> (1994 and reviewed in 2000) notes, "The therapeutic efficacy of miscellaneous topical agents (e.g., sugar, vitamins, elements, hormones, other agents), growth factors, and skin equivalents has not yet been sufficiently established to warrant recommendation of these agents at this time (strength of evidence = C.)" Level C evidence requires one of the following: (1) results of one controlled trial; (2) results of at least two case series/descriptive studies on pressure ulcers in humans; or

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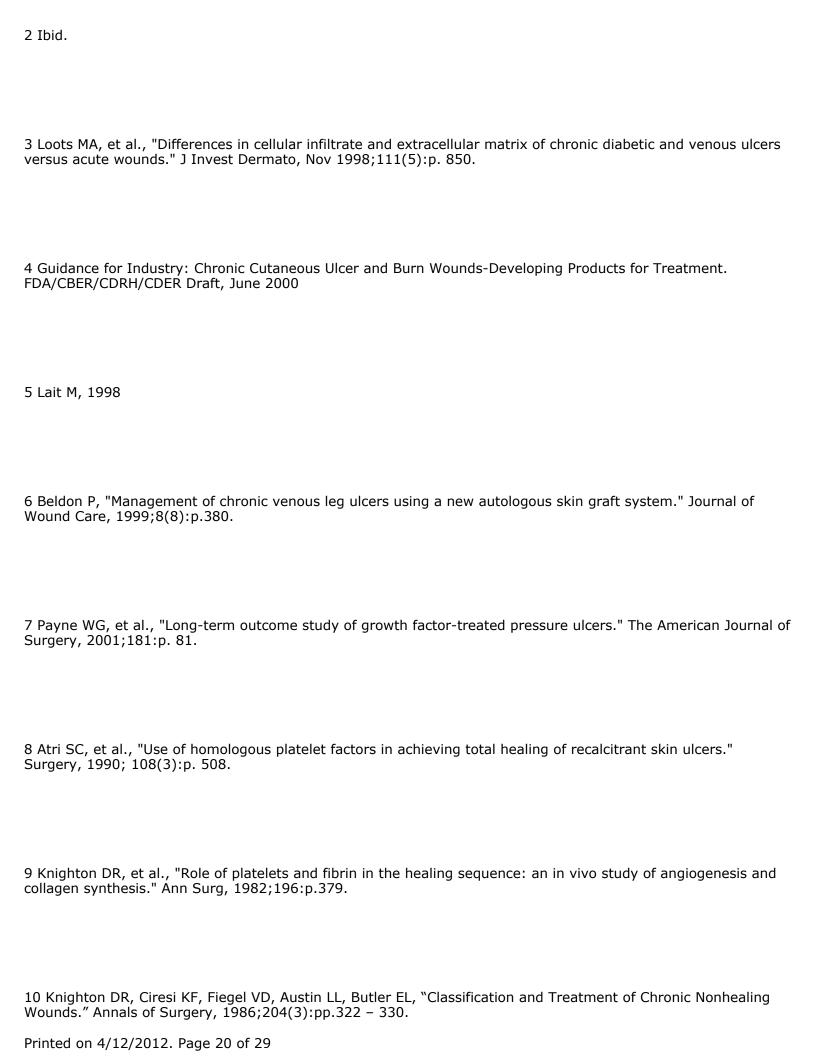
(3) expert opinion.

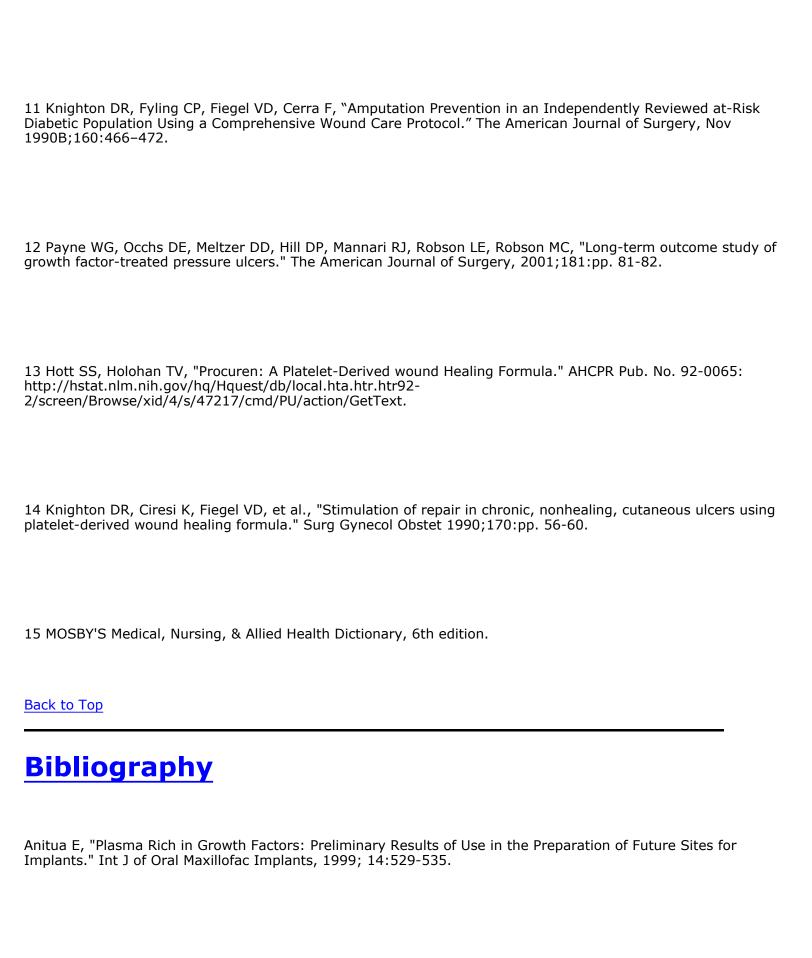
expert opinion.

6. Professional Society Position Statements We were not provided nor were we able to identify any professional society position papers. 7. Expert Opinion Six companies contacted CMS. Upon request, CMS met with three of these companies after the national coverage determination process was started (Cytomedix, Medtronic, and COBE) to discuss the current state of wound healing with autologous, blood-derived wound care products for chronic, non-healing wounds. The remaining three companies, Harvest Technologies Corporation, Safeblood Technologies, and Innovative Medical Technologies, submitted information for CMS review. We also received comments from some individual providers. Generally, they were all supportive of the promise of the product and procedure. However, two of the companies, Cytomedix and Medtronic, cautioned CMS that they did not believe sufficient evidence was available for CMS to make a decision and informed us they were planning on conducting trials using autologous platelet rich plasmas. Safeblood technologies submitted a position statement, an overview of the Safeblood procedure, and an unpublished report of a retrospective case series written by RA Dellinger, DPM. The documents were assessed as lower quality evidence with significant potential bias and confounding, using the critreia in Section VI of this document. VIII. CMS Analysis National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under section 1869(f)(1)(B) of the Social Security Act (the Act). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member" (section 1862(a)(1)(A) of the Act). a. Platelet rich plasma





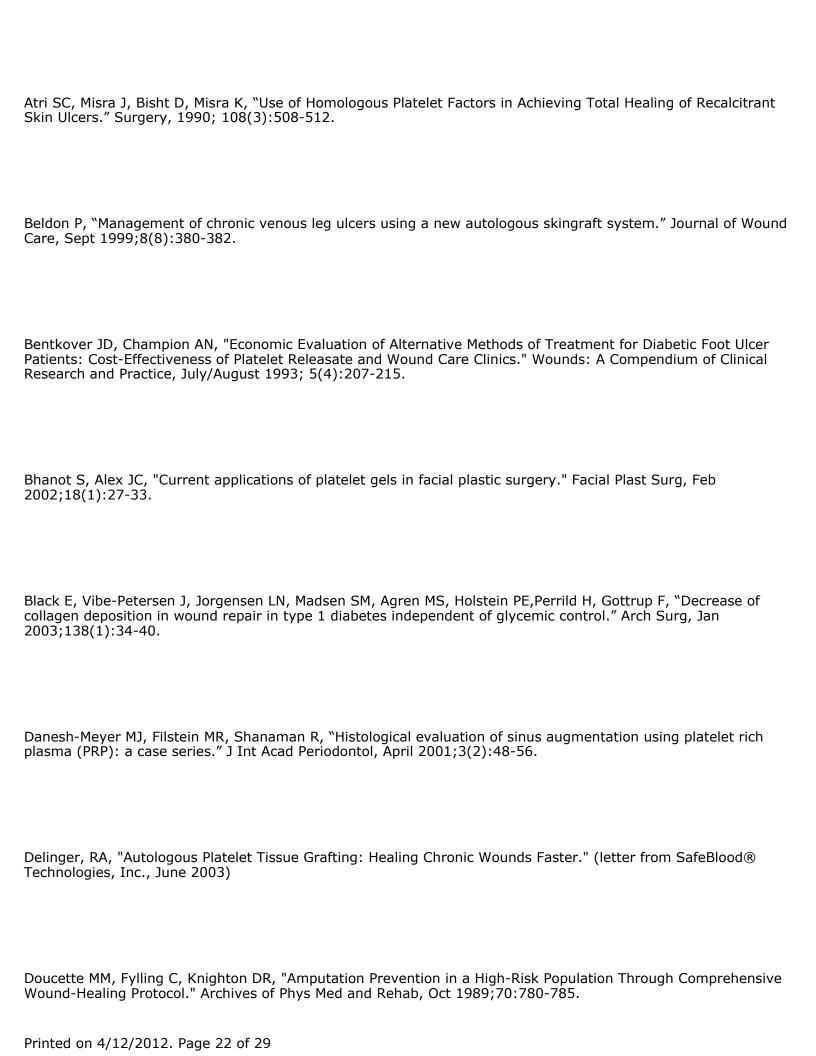


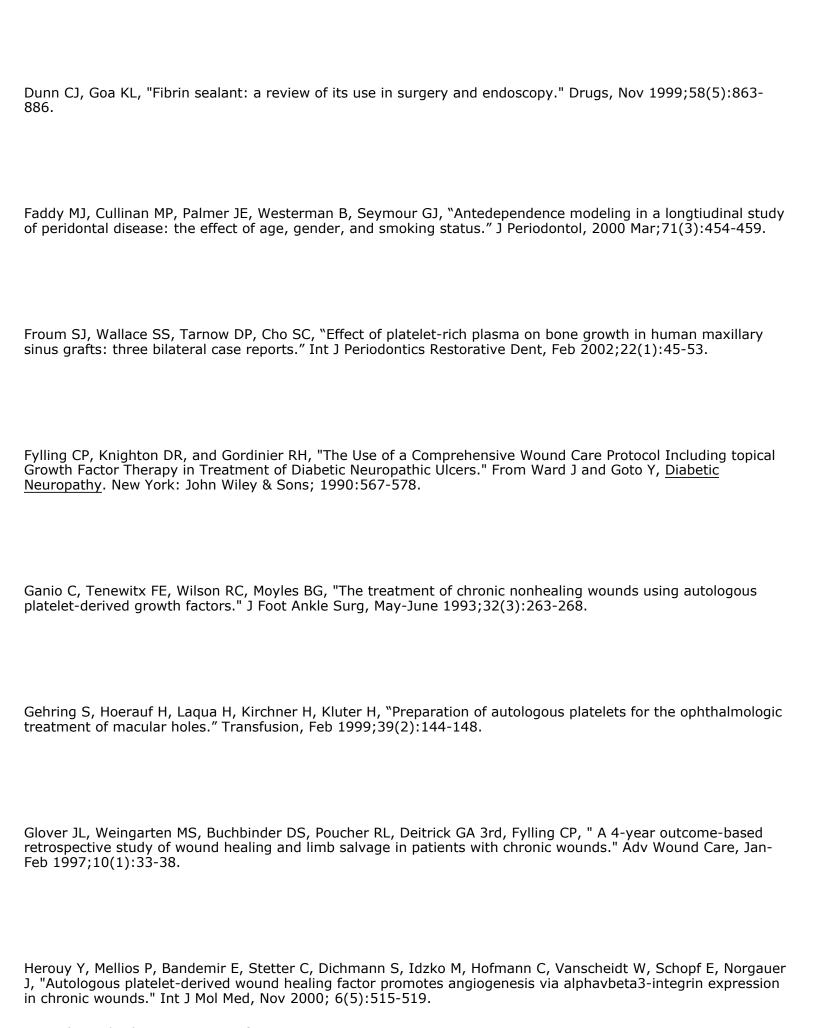


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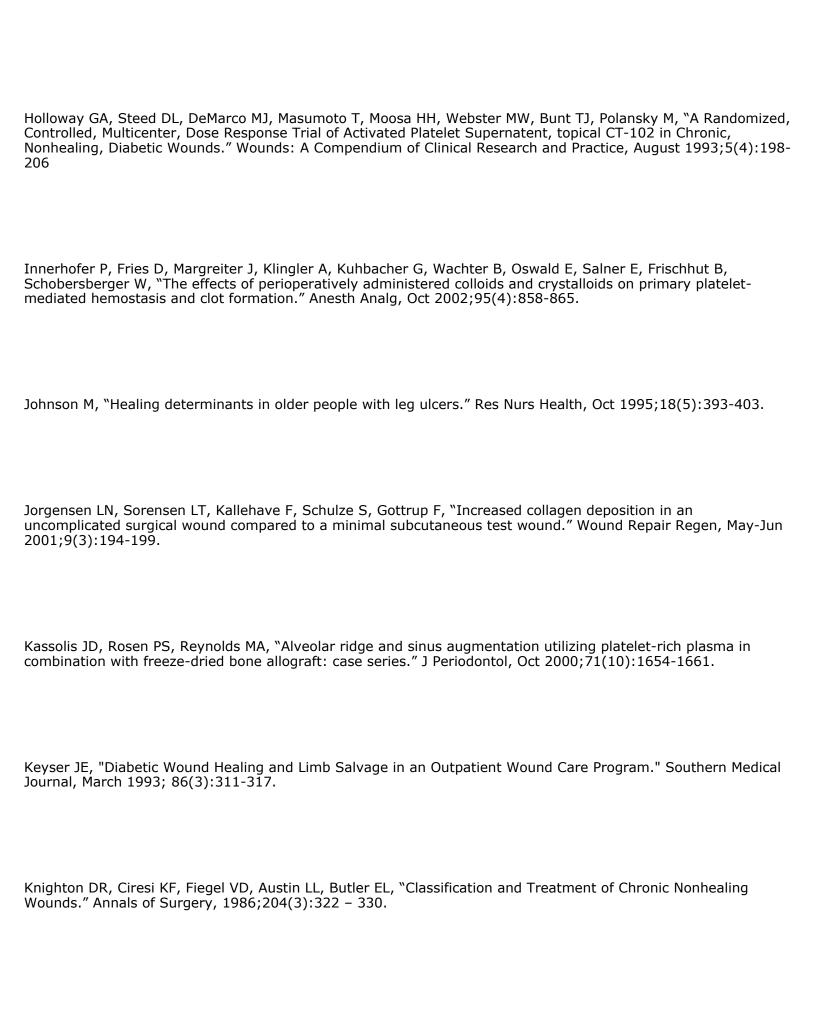
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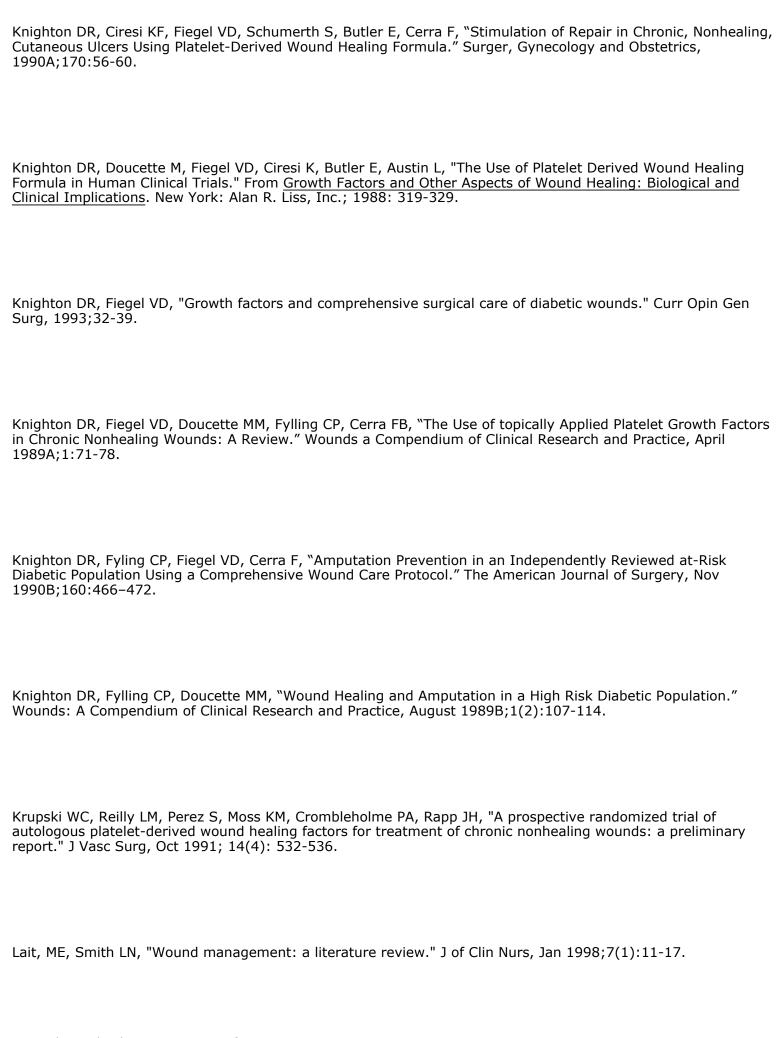
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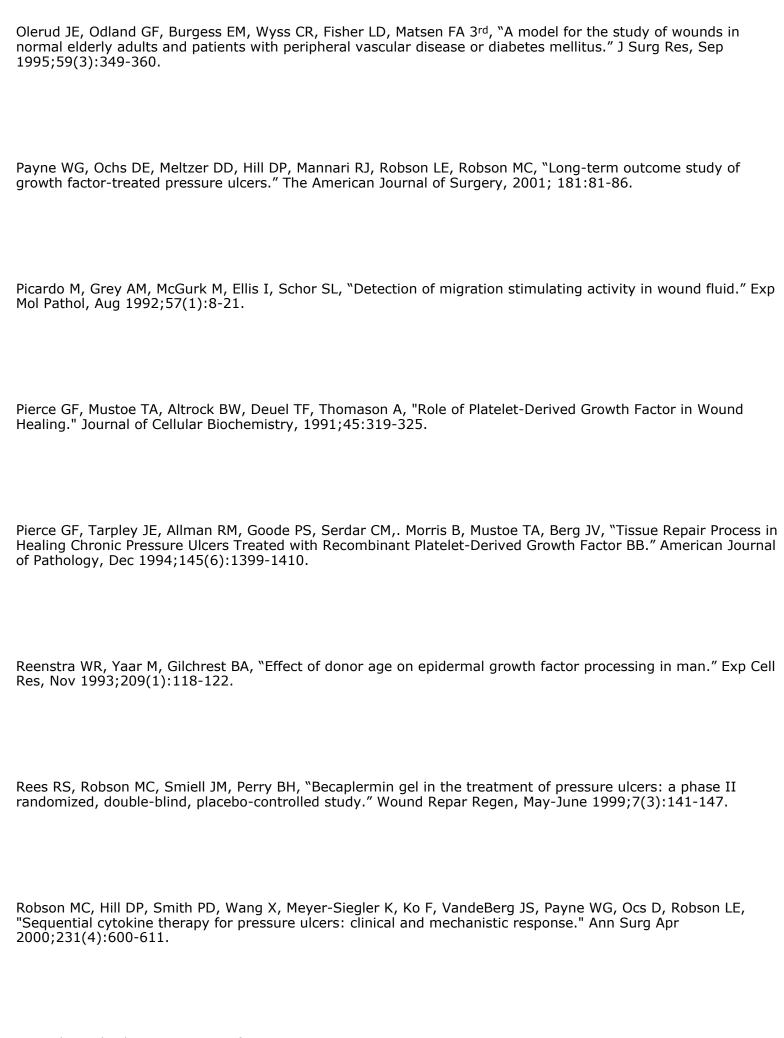


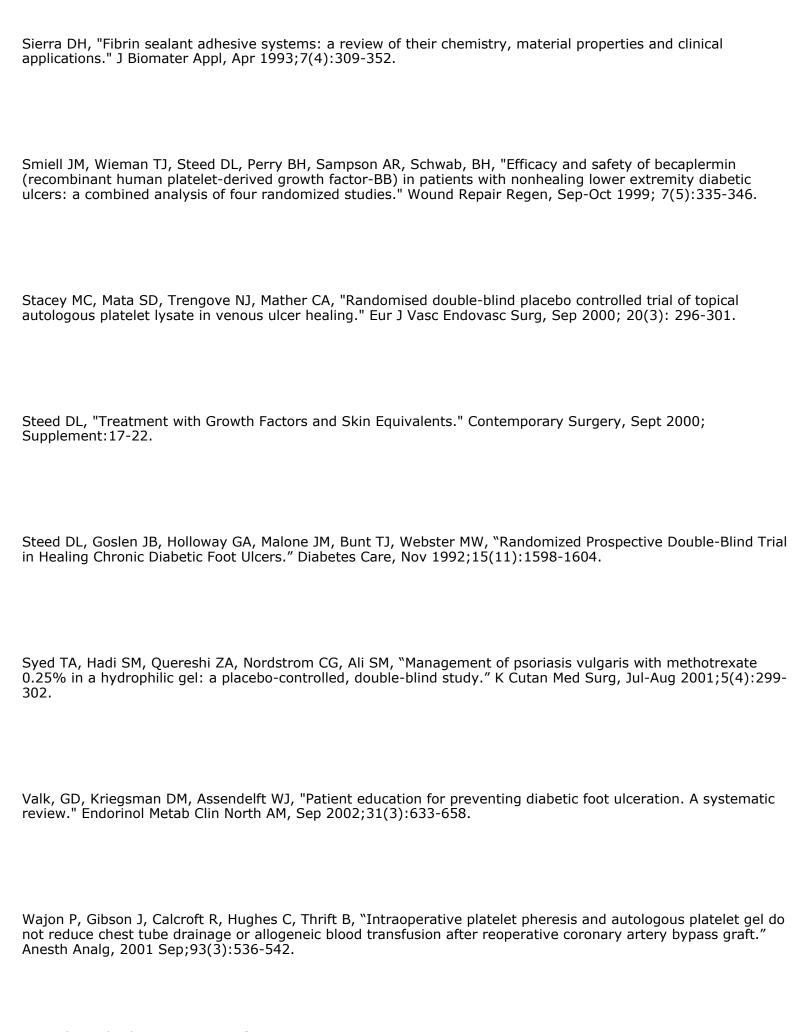
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